Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 5103–5105

β-Lactams in synthesis: short syntheses of cobactin analogs

Andrew J. Walz[a] and Marvin J. Miller[a,b,*]

[a]*Department of Chemistry and Biochemistry, University of Notre Dame, 251 Nieuwland Science Hall, Notre Dame, IN 46556, USA*
[b]*Leibniz Institute for Natural Product Research and Infection Biology, Hans Knoell Institute, Beutenbergstrasse 11a, 07745 Jena, Germany*

Received 5 March 2007; revised 11 May 2007; accepted 14 May 2007
Available online 18 May 2007

Abstract—Mycobactins facilitate assimilation of iron by mycobacteria. Synthetic analogs with structural variation of the cobactin component have potent anti-TB activity. A new method for the synthesis of cobactin analogs is presented. The key process involves single-step coupling reactions between an amine of a cyclic (L)-lysine derived hydroxamic acid with cyanide activated β-lactams.

Mycobactins are the lipid bound siderophores used by mycobacteria, including *Mycobacteria tuberculosis*, to sequester iron that is essential for their survival and virulence.[1] While all the mycobactins are structurally similar, subtle variations are responsible for remarkable mycobacterial strain selectivity. Thus, the use of non-TB produced mycobactins and mycobactin analogs as anti-tuberculosis (anti-TB) agents was first postulated by Snow.[2] Results from our laboratories have confirmed Snow's hypothesis by demonstrating that synthetic mycobactin S,[3] the natural growth promoting mycobactin utilized by *M. smegmatis*, *inhibits* the growth of *M. tuberculosis*, although it differs only in the configuration at the β-hydroxy butyrate constituent from mycobactin T, the siderophore produced and used by *M. tuberculosis* for growth *promotion*. As shown in Figure 1, synthetic replacement of the usual β-hydroxy acid of the cobactin component with a β-amino acid produced non-natural mycobactin analogs[4] that are even more potent anti-TB agents.

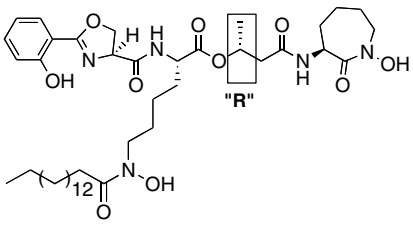
The established retro-synthetic plan for mycobactin analogs **1** ($R_1 = H$, X and Y = variable) proceeded with an initial disconnection that yielded two fragments, mycobactic acid **2** and cobactin analogs **3** (Fig. 2). As indicated above, modification of the cobactin component dramatically affects the biological activity of mycobactin analogs. Preparation of cobactin analogs **3** ($R_1 = OBn$, $R_2 = TBDPS$) relied upon the coupling of the free amine derived from removal of the Cbz group from **4** ($R_2 = TBDPS$) with acids **5** ($R_1 = OBn$). These acids were obtained from the LiOH-mediated opening of β-lactams **6** ($R_1 = OBn$). Attempts to utilize this synthetic route were not routinely efficient.[4] Partial loss of the TBDPS protecting group during EDC/HOAt-mediated coupling reactions of acids **5** and the free amine of **4** to obtain cobactins **3** ($R_1 = OBn$) was observed and reprotection was necessary. The considerable interest in the syntheses of mycobactin analogs for further structure–activity relationship (SAR) studies was anticipated to be facilitated by development of an improved and efficient route to the key cobactin components. Herein, we disclose a one-pot coupling reaction between N1–Boc/N1–OBn butyrate-derived β-lactams **6** with the free amine of **4** (**4a**) to generate cobactin analogs **3** ($R_1 = OBn$ or Boc, $R_2 = H$) directly for subsequent syntheses of mycobactin analogs.

The coupling of amines of amino acid esters and alcohols to N1-carbamate-protected β-lactams has been reported with[5–9] and without[10–12] the utilization of either azide or cyanide anions as the β-lactam activators. A macrolactamization using this type of methodology has been reported by Romo and co-workers in the synthesis of (−)-Pateamine A.[13] There is a report concerning the opening of the N1–OBn β-lactam derived from α-benzyl-β-hydroxypropionic acid with a tenfold excess of methyl amine in methanol.[14] Our earlier attempts with direct reactions of optically pure amino acid derivatives and an N1–OBn β-lactam resulted in partial racemization.[15]

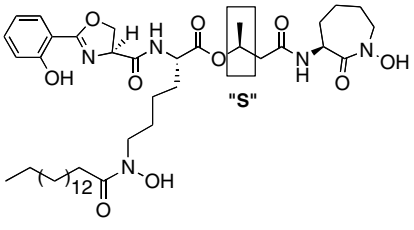
To initiate the syntheses of cobactin analogs, a variation of the synthesis of the Cbz-protected cyclic hydroxamic

* Corresponding author. E-mail: mmiller1@nd.edu

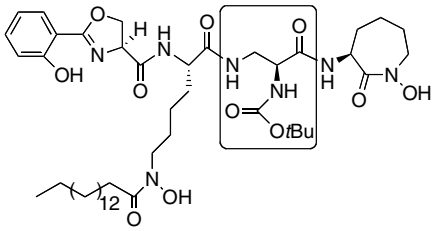
0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.05.085



Mycobactin T, a growth promoter for *M. tuberculosis*



Mycobactin S, a growth promoter for *M. smegmatis*. Effects greater than 99% inhibition of the growth of *M. tuberculosis* H37Rv at 12.5 μg/mL



Diaminoproprionate analog, Growth inhibitor of *M. tuberculosis* H37Rv, with MIC 0.2 μg/mL

Figure 1. Structures of mycobactins and a synthetic β-amino acid analog with anti-TB activity.

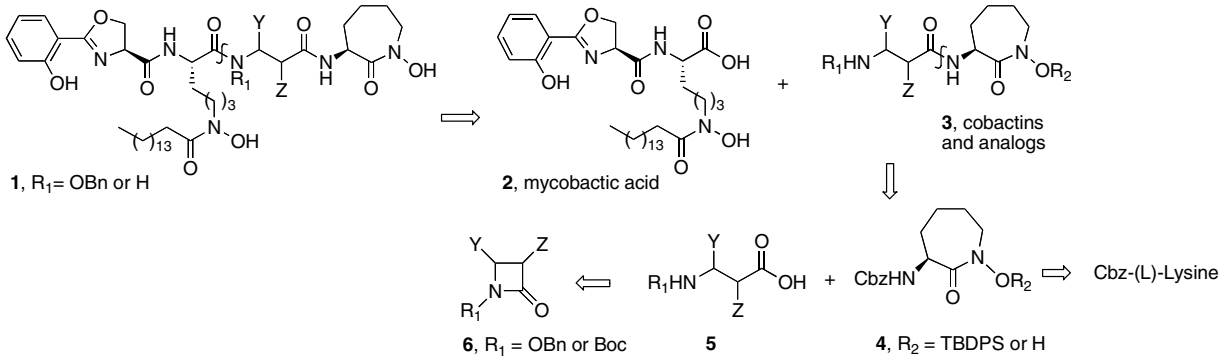
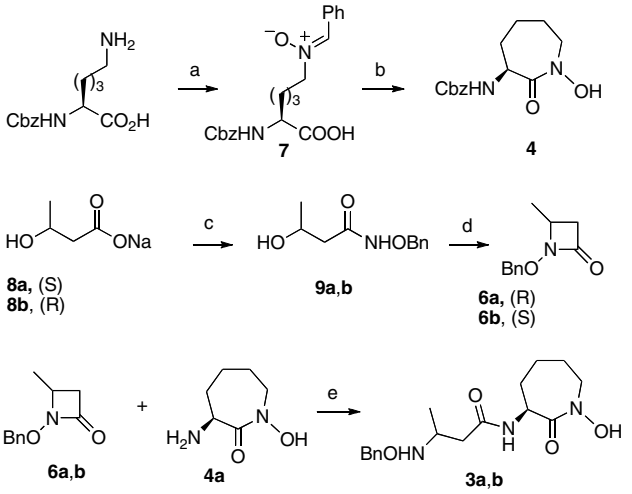


Figure 2. Retrosynthetic analysis of mycobactin and cobactin analogs.

acid (**4**) was derived from the previously reported efficient indirect oxidation method.[16] Thus, condensation of Cbz-(L)-lysine with freshly distilled benzaldehyde was followed by dry *m*-CPBA oxidation of the intermediate imine to form an oxaziridine ring. TFA-mediated isomerization of the oxaziridine led to nitrone **7** in good overall yield from the starting protected amino acid (Scheme 1). The TFA reaction did result in some hydrolysis of the nitrone so the yield was improved by subsequent readdition of benzaldehyde. Formation of the precyclization hydroxylamine HCl salt was accomplished by the action of 1.1 equiv of hydroxylamine hydrochloride on nitrone **7** at elevated temperatures in methanol. Cyclization was accomplished using 1.1 and 1.2 equiv of EDC and HOAt, respectively, under basic, high dilution conditions. After reverse phase chromatography, hydroxamic acid **4** was obtained in 55% overall yield from nitrone **7**.

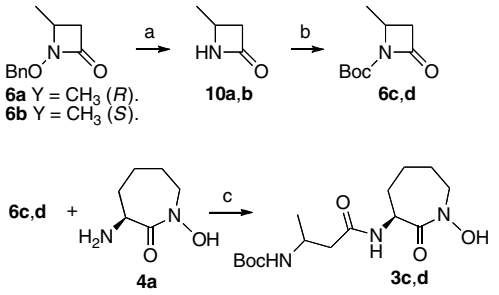
The synthesis of enantiopure 4-(methyl)-1-(benzyloxy)-2-azetidinones was accomplished as also shown in Scheme 1. Starting with commercially available (*R*) and (*S*) 3-hydroxybutyric acid sodium salts (Aldrich), hydroxamic acids **8a** and **8b** were formed separately by EDC/DMAP coupling with *O*-benzylhydroxylamine hydrochloride. Cyclization to the corresponding azetidinones was accomplished with triphenylphosphine, carbon tetrachloride and triethylamine in dry acetonitrile to give β-lactams **6a**,**b**.[17]

Initial attempts at coupling β-lactams **6a**,**b** with the amine of **4a** to give cobactin analogs **3a**,**b** using an ex-



Scheme 1. Reagents and conditions: (a) (1) PhCHO, KOH, MS, MeOH, rt, 16 h; (2) *m*-CPBA, MeOH, 0 °C to rt, 4 h; (3) TFA, CH_2Cl_2, rt, 1 h; (4) PhCHO, EtOAc, 0 °C to rt, (66% overall); (b) (1) $NH_2OH(HCl)$, MeOH, 65 °C, 20 min; (2) EDC, HOAt, $NaHCO_3$, CH_3CN, DMF, rt, 48 h, (55%); (c) $BnONH_2(HCl)$, EDC, DMAP, H_2O, THF or DMF, rt, 16 h, (80–90%); (d) PPh_3, CCl_4, TEA, CH_3CN, rt, 16 h, (75–85%); (e) TMSCN, TBAF, CH_3CN, rt, 48 h, (75%).

cess of flame dried KCN and catalytic 18-crown-6 ether in anhydrous acetonitrile at room temperature failed. Heating the reaction led to decomposition of the material. An effective alternative was the use of hypervalent cyano-silicates as nucleophiles according to the protocol reported by Smith and DeShong.[18] As was described,



Scheme 2. Reagents and conditions: (a) SmI_2, H_2O, THF, 0 °C to rt, 3 h, (60–65%); (b) $(BOC)_2O$, DMAP, THF, rt, 16 h, (80–89%); (c) KCN, 18-crown-6 ether, CH_3CN, rt, 24–48 h, (79–86%).

the in situ generation of the hypervalent cyano-silicate was accomplished with TMSCN and TBAF. Stirring the reagents in the presence of the cyclic aminohydroxamic acid and the β-lactams led to the efficient formation of the desired cobactin analogs as single diastereomers.

In order to synthesize amine terminated cobactin analogs, attempts at reduction of the benzylated hydroxylamine functionalities of **3a**,**b** were made. Utilization of H_2 and 10% Pd–C or Pearlman's catalyst for this reduction led to complex reaction mixtures. Therefore, reduction of the N1–OBn functionality was accomplished on β-lactams **6a**,**b** followed by Boc protection. Utilization of these β-lactams in the cyanide-promoted coupling reactions provided the desired amine terminated cobactin analogs.

Direct cleavage of the N–O bond of substituted 1-(benzyloxy)-2-azetidinones cannot be easily accomplished using hydrogenation or other more common N–O bond reduction protocols. Titanium(III) chloride has been used in a two step procedure developed earlier in our group.[19] Romo subsequently reported a samarium diiodide-mediated reduction of the N–O bond of a functionalized 1-(benzyloxy)-2-azetidinone.[13] The procedure was adapted from the work of Keck and co-workers.[20] Use of the samarium protocol allowed elaboration of the 4-(methyl)-1-(benzyloxy)-2-azetidinones **6a**,**b** to their Boc-protected coupling precursors **6c**,**d** as shown in Scheme 2. SmI_2 N–O bond reductions of these substrates proceeded in 60–65% yield after chromatography. Boc protection of the intermediate 4-(methyl)-1*H*-2-azetidinones led to the desired products in acceptable yields.

With the necessary components in hand, coupling reactions between the amino hydroxamic acid **4a** and the β-lactams **6c**,**d** were successfully accomplished, as also shown in Scheme 2, to give the desired separate diastereomers of cobactin analogs **3c**,**d**.

In summary, synthetic methodology has been disclosed that allows for the one-pot coupling of N1–Boc/N1–OBn butyrate-derived β-lactams with an amine in the presence of unprotected hydroxamic acids to form new cobactin analogs. The incorporation of these compounds into full mycobactin analogs and their biological activity is under consideration.

Acknowledgments

This research was supported by the NIH (AI054193). M.J.M. gratefully acknowledges the kind hospitality of the HKI and the University of Notre Dame for a sabbatical opportunity.

References and notes

1. (a) Vergne, A. F.; Walz, A. J.; Miller, M. J. *Nat. Prod. Rep.* **2000**, *17*, 99–116; (b) Ratledge, C. *Tuberculosis* **2004**, *84*, 110–130.
2. Snow, G. A. *Bacteriol. Rev.* **1970**, *34*, 99–125.
3. Hu, J.; Miller, M. J. *J. Am. Chem. Soc.* **1997**, *119*, 3462–3468.
4. Xu, Y.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 4314–4322.
5. Palomo, C.; Aizpurua, J. M.; Cuevas, C. *Chem. Commun.* **1994**, 1957–1958.
6. Palomo, C.; Aizpurua, J. M.; Cuevas, C.; Mielgo, A.; Galarza, R. *Tetrahedron Lett.* **1995**, *36*, 9027–9030.
7. Palomo, C.; Aizpurua, J. M.; Galarza, R.; Meilgo, A. *Chem. Commun.* **1996**, 633–634.
8. Palomo, C.; Oiarbide, M.; Bindi, S. *J. Org. Chem.* **1998**, *63*, 2469–2474.
9. Cundy, D. J.; Donohue, A. C.; McCarthy, T. D. *Tetrahedron Lett.* **1998**, *39*, 5125–5128.
10. Ojima, Y.; Sun, C. M.; Park, Y. H. *J. Org. Chem.* **1994**, *59*, 1249–1250.
11. Ojima, Y.; Wang, T.; Delaloge, F. *Tetrahedron Lett.* **1998**, *39*, 3663–3666.
12. Mostowicz, D.; Chmielewski, M. *Carbohydr. Res.* **1994**, *257*, 137–143.
13. Romo, D.; Rzasa, R. M.; Shea, H. A.; Park, K.; Lanhgenhan, J. M.; Sun, L.; Akheizer, A.; Liu, J. O. *J. Am. Chem. Soc.* **1998**, *120*, 12237–12254.
14. Jin, Y.; Kim, D. H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3515–3518.
15. Walz, A. J.; Miller, M. J. *Org. Lett.* **2002**, *4*, 2047–2050.
16. Lin, Y.-M.; Miller, M. J. *J. Org. Chem.* **1999**, *64*, 7451–7458.
17. Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 7026–7032.
18. Soli, E. D.; Manoso, A. S.; Patterson, M. C.; DeShong, P.; Favor, D. A.; Hirschmann, R.; Smith, A. B., III. *J. Org. Chem.* **1999**, *64*, 3171–3177.
19. Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1980**, *45*, 410–415.
20. Keck, G. E.; McHardy, S. F.; Wager, T. T. *Tetrahedron Lett.* **1995**, *36*, 7419–7422.